PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/18, 31/33, 31/495, 31/535, 31/54, 31/445, 31/40, 31/335, 31/38, 31/55, 31/47, 31/42, 31/425

A1

(11) International Publication Number: **WO 96/40101**

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/EP96/02418

(22) International Filing Date: 4 June 1996 (04.06.96)

(30) Priority Data:
08/475,166 7 June 1995 (07.06.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/475,166 (CIP)
Filed on 7 June 1995 (07.06.95)

(71) Applicant *(for all designated States except US)*: CIBA-GEIGY AG [CH/CH]; Klybeckstrasse 141, CH-4002 Basle (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MACPHERSON, Lawrence, Joseph [US/US]; R.D. 1, Box 25B, Perryville Road, Hampton, NJ 08827 (US). PARKER, David, Thomas [US/US]; 291 East Northfield Road, Livingston, NJ 07039 (US).

(74) Common Representative: CIBA-GEIGY AG; Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).

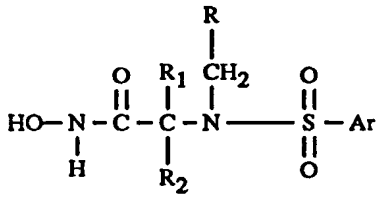
(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CERTAIN ARYLSULFONAMIDO-SUBSTITUTED HYDROXAMIC ACIDS FOR THE TREATMENT OF CERTAIN TUMORS

(57) Abstract

The invention relates to the use of compounds of formula (I) wherein Ar, R, R_1 and R_2 are as defined in the specification, (for the manufacture of a medicament) for the treatment of a tumor selected from human breast carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, prostate carcinoma, skin carcinoma and ovarian carcinoma.



(I)

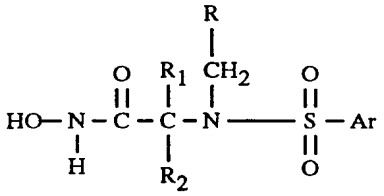
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

Certain arylsulfonamido-substituted hydroxamic acids for the treatment of certain tumors

The present invention relates to use of a compound of formula I



(I)

(a) wherein

Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_{10}-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy) lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl or N-acyl(hexahydroazepinyl, piperidyl or pyrrolidinyl), C_5-C_{10}-oxacycloalkyl, C_5-C_{10}-thiacycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-cycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-thiacycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-

oxacycloalkyl, (amino, mono- or dialkylamino or acylamino)-C_5-C_{10}-cycloalkyl, 2-oxo(pyrrolidinyl, piperidyl or hexahydroazepinyl), (carbocyclic or heterocyclic aryl)-(thio, sulfinyl or sulfonyl)-lower alkyl;

R_2 is hydrogen or lower alkyl;

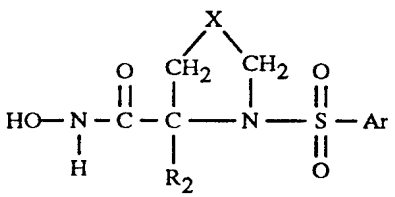
(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof; (for the manufacture of a medicament) for the treatment of a tumor selected from human breast carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, prostate carcinoma, skin carcinoma and ovarian carcinoma;

further to some new compounds of the formula I, a process for the preparation of these latter compounds, to pharmaceutical compositions comprising these latter compounds, to the use of these latter compounds for the therapeutic treatment of the human or animal body or for the manufacture of a pharmaceutical composition.

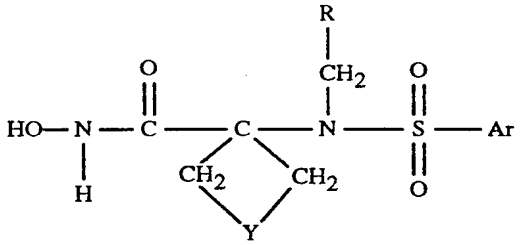
The compounds of formula I defined under (b) above can be represented by formula Ia



(Ia)

wherein X represents methylene or 1,2-ethylene each unsubstituted or substituted by lower alkyl, or X represents oxygen, sulfur, or 1,2-phenylene; and Ar and R_2 have meaning as defined above.

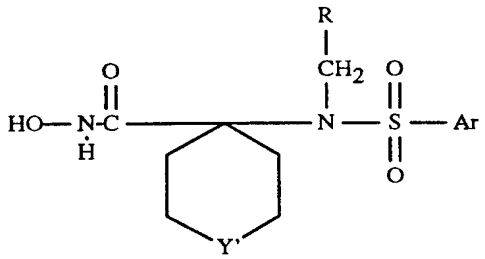
The compounds of formula I defined under (c) above can be represented by formula Ib



(Ib)

wherein Y is a direct bond, C_1-C_4-straight chain alkylene optionally substituted by lower alkyl, CH_2OCH_2, CH_2SCH_2, 1,2-phenylene, CH_2-1,2-phenylene or $CH_2N(R_6)$-CH_2 in which R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, aroyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocylic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; and Ar and R have meaning as defined above.

A preferred embodiment of the compounds of formula Ib relates to the compounds of formula Ic



(Ic)

in which Y' represents oxygen, sulfur, a direct bond, methylene or methylene substituted by lower alkyl, or NR_6; R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; Ar and R have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof.

Preferred are said compounds of formula I, Ia, Ib and Ic wherein Ar is monocyclic carbocyclic aryl such as phenyl or phenyl mono-, di- or tri-substituted by C_1-C_{10}-alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, C_3-C_7-cycloalkyl-lower alkoxy, (lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or C_3-C_7-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino or mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is heterocyclic monocyclic aryl such as thienyl or thienyl substituted by lower alkyl; the other symbols have meaning as defined; pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_{10}-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; or Ar is phenyl substituted by C_3-C_7-cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C_3-C_7-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenylyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; biphenylyl-lower alkyl

wherein biphenylyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; (pyridyl, thienyl, quinolinyl or thiazolyl)-lower alkyl, trifluoromethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; pyridyl; thienyl, biphenylyl; biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; trifluoromethyl; C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl; hydroxy-lower alkyl; lower alkanoyloxy-lower alkyl; lower alkoxy-lower alkyl; (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl- or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C_5-C_{10}-oxacycloalkyl; C_5-C_{10}-thiacycloalkyl; (hydroxy- or oxo-) C_5-C_{10}-cycloalkyl; (hydroxy- or oxo-) C_5-C_{10}-thiacycloalkyl; (hydroxy- or oxo-) C_5-C_{10}-oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C_5-C_{10}-cycloalkyl; phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl, or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl, thienyl and furanyl, each unsubstituted or substituted by lower alkyl;

R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, benzyloxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Especially preferred are the compounds of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_7-alkoxy, hydroxy, phenyl-lower alkoxy, C_3-C_7-cycloalkyl-lower alkoxy, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen; lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenylyl; biphenylyl-lower alkyl; (pyridyl or thienyl)-lower alkyl; trifluoromethyl; C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl; (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl; hydroxy-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower

alkylpiperidyl)-lower alkyl;

R_1 is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy; biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; C_3-C_{10}-cycloalkyl; C_3-C_7-cycloalkyl-lower alkyl; hydroxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkyl-piperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl- or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C_5-C_{10}-oxacycloalkyl; C_5-C_{10}-thiacycloalkyl; (hydroxy- or oxo-) C_5-C_{10}-cycloalkyl; (hydroxy- or oxo-) C_5-C_{10}-thiacycloalkyl; (hydroxy- or oxo-) oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C_5-C_{10}-cycloalkyl; phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thienyl and furanyl, each unsubstituted or substituted by lower alkyl;

R_2 is hydrogen or lower alkyl;

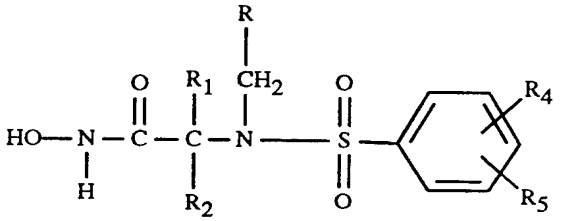
(b) or wherein R and R_1 together with the chain to which they are attached form a thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane; thia-cyclohexane; and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R

have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A particular embodiment of the invention relates to the use of a compound of formula II



(II)

wherein

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_5-C_8-cycloalkyl, C_5-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, piperidyl, N-lower alkylpiperidyl, or acylamino-lower alkyl represented by R_3-CONH-lower alkyl, pyrrolidinyl, hexahydroazepinyl or N-lower alkyl (pyrrolidinyl or hexahydroazepinyl), C_5-C_7-oxacycloalkyl, C_5-C_7-thiacycloalkyl, hydroxy or oxo-cyclohexyl, (amino, mono- or di-lower alkylamino) cyclohexyl or

2-oxohexahydroazepinyl; phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl; heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thienyl and furanyl, each unsubstituted or substituted by lower alkyl;

R_2 is hydrogen;

R_3 in R_3-CONH-lower alkyl is lower alkyl, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)-lower alkyl;

R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

R_5 is hydrogen, lower alkyl or halogen;

ør R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;

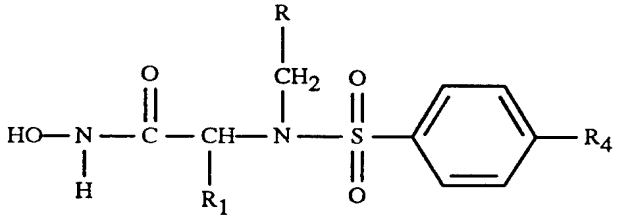
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the invention relates to the use of a compound of formula II wherein R and R_1 together with the chain to which they are attached form an 1,2,3,4-tetrahydro-isoquinoline, piperidine, thiazolidine or pyrrolidine ring; and R_2, R_4 and R_5 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof. Such compounds correspond to compounds of formula Ia wherein Ar is optionally substituted phenyl as defined above.

Another preferred embodiment of the invention relates to the use of a compound of formula II wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from cyclohexane, cyclopentane, oxacyclohexane, thiacyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or by lower alkylsulfonyl; and R,

R_4 and R_5 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof. Such compounds correspond to compounds of formula Ib wherein Ar is optionally substituted phenyl as defined above.

Particularly preferred is the use of a compound of formula III



(III)

wherein R represents lower alkyl, trifluoromethyl, C_5-C_7-cycloalkyl, (oxa or thia)-C_4-C_5-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R_1 represents hydrogen, lower alkyl, C_5-C_8-cycloalkyl, monocyclic carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl-lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, di-lower alkylamino-lower alkyl, (N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino)-lower alkyl, C_5-C_7-oxacycloalkyl, (hydroxy, oxo or di-lower alkylamino) cyclohexyl, R_3-CONH-lower alkyl, phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl, heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyridyl, imidazolyl, thienyl and furanyl, each unsubstituted or substituted by lower alkyl; R_3 represents lower alkyl, carbocyclic aryl, heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; R_4 represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Further preferred are compounds of formula III wherein R represents monocyclic carbocyclic aryl or monocyclic heterocyclic aryl; R_1 and R_4 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof.

More particularly preferred are said compounds of formula III wherein R represents

heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents lower alkyl, cyclohexyl, 2- or 3-tetrahydrofuranyl,(phenyl-, thienyl- or furanyl-)thiomethyl, or R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; and R_4 represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A further preferred embodiment relates to the use of a said compound of formula III wherein R represents 2-, 3- or 4-pyridyl or phenyl; R_1 represents C_1-C_4-alkyl, cyclohexyl, 2- or 3-tetrahydrofuranyl, or R_3-CONH-C_1-C_4-alkyl wherein R_3 represents di-C_1-C_4-alkylamino-C_1-C_4-lower alkyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Particularly preferred are said compounds of formula III wherein R represents 3-pyridyl or 4-pyridyl; R_1 represents isopropyl, cyclohexyl or 2-tetrahydrofuranyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention relates to the use of a compound of formula III wherein R represents pyridyl, pyridyl substituted by lower alkyl, phenyl, or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents (phenyl-, thienyl- or furanyl-) thio-C_1-C_4-alkyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt therof.

Further preferred are said compounds of formula III wherein R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents (phenyl)-thiomethyl, (2-thienyl)-thiomethyl or (2-furanyl)-thiomethyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

The invention relates especially to the use of the specific compounds described in the

examples, pharmaceutically acceptable prodrug derivatives thereof and pharmaceutically acceptable salts thereof, and in particular to the use of the specific compounds described in the examples and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable prodrug derivatives are those that may be convertible by solvolysis or under physiological conditions to the free hydroxamic acids of the invention and represent such hydroxamic acids in which the CONHOH group is derivatized in form of an O-acyl or an optionally substituted O-benzyl derivative. Preferred are the optionally substituted O-benzyl derivatives.

The compounds of the invention depending on the nature of the substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and enantiomers are encompassed by the instant invention.

Preferred are the compounds of the invention wherein the asymmetric carbon in the above formulae (to which are attached R_1 and/or R_2) corresponds to that of a D-aminoacid precursor and is assigned the (R)-configuration.

The general definitions used herein have the following meaning within the scope of the present invention, unless otherwise specified.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms, and represents for example methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

A lower alkoxy (or alkyloxy) group preferably contains 1-4 carbon atoms, advantageously 1-3 carbon atoms, and represents for example ethoxy, propoxy, isopropoxy, or most advantageously methoxy.

Halogen (halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Mono- or poly-halo-lower alkyl represents lower alkyl preferably substituted by one, two

or three halogens, preferably fluoro or chloro, e.g. trifluoromethyl or trifluoroethyl.

Aryl represents carbocyclic or heterocyclic aryl.

Prodrug acyl derivatives are preferably those derived from an organic carbonic acid, an organic carboxylic acid or a carbamic acid.

An acyl derivative which is derived from an organic carboxylic acid is, for example, lower alkanoyl, phenyl-lower alkanoyl or unsubstituted or substituted aroyl, such as benzoyl.

An acyl derivative which is derived from an organic carbonic acid is, for example, alkoxycarbonyl, especially lower alkoxycarbonyl, which is unsubstituted or substituted by carbocyclic or heterocyclic aryl or is cycloalkoxycarbonyl, especially C_3-C_7-cycloalkyloxycarbonyl, which is unsubstituted or substituted by lower alkyl.

An acyl derivative which is derived from a carbamic acid is, for example, amino-carbonyl which is substituted by lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, carbocyclic or heterocyclic aryl, lower alkylene or lower alkylene interrupted by O or S.

Prodrug optionally substituted O-benzyl derivatives are preferably benzyl or benzyl mono-, di-, or tri-substituted by e.g. lower alkyl, lower alkoxy, amino, nitro, halogen and/or trifluoromethyl.

Carbocyclic aryl represents monocyclic or bicyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, hydroxy, halogen, cyano, trifluoromethyl, lower alkylenedioxy and oxy-C_2-C_3-alkylene; or 1- or 2-naphthyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C_2-C_3-alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy-C_2-C_3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is phenyl or phenyl monosubstituted by lower alkoxy, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl monosubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by e.g. lower alkyl or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 2- or 3-pyridyl. Thienyl represents 2- or 3-thienyl, advantageously 2-thienyl. Quinolinyl represents preferably 2-, 3- or 4-quinolinyl, advantageously 2-quinolinyl. Isoquinolinyl represents preferably 1-, 3- or 4-isoquinolinyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl. Imidazolyl is preferably 4-imidazolyl.

Preferably, heterocyclic aryl is pyridyl, quinolinyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen; and in particular pyridyl.

Biaryl is preferably carbocyclic biaryl, e.g. biphenyl, namely 2, 3 or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano.

C_3-C_{10}-Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 10 ring carbons and is advantageously cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl optionally substituted by lower alkyl.

(Oxa or thia)-C_3-C_6-cycloalkyl represents a saturated cyclic radical wherein 1 or 2, preferably 1, oxygen or sulfur atom(s) and preferably 4-5 carbon atoms form a ring, e.g. tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl or tetrahydrothienyl.

Oxa-cyclohexane means tetahydropyran, and thia-cyclohexane means tetrahydrothiopyran.

Carbocyclic aryl-lower alkyl represents preferably straight chain or branched aryl-C_1-C_4-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted on phenyl ring as defined under carbocyclic aryl above, advantageously optionally substituted benzyl.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C_1-C_4-alkyl in which heterocyclic aryl has meaning as defined above, e.g. 2-, 3- or 4-pyridylmethyl or (2-, 3- or 4-pyridyl)-(ethyl, propyl or butyl); or 2- or 3-thienylmethyl or (2- or 3-thienyl)-(ethyl, propyl or butyl); 2-, 3- or 4-quinolinylmethyl or (2-, 3- or 4-quinolinyl)-(ethyl, propyl or butyl); or 2- or 4-thiazolylmethyl or (2- or 4-thiazolyl)-(ethyl, propyl or butyl).

Cycloalkyl-lower alkyl represents e.g. (cyclopentyl- or cyclohexyl)-(methyl or ethyl).

Biaryl-lower alkyl represents e.g. 4-biphenylyl-(methyl or ethyl).

Acyl is derived from an organic carboxylic acid, carbonic acid or carbamic acid.

Acyl represents e.g. lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkoxycarbonyl, aroyl, di-lower alkylaminocarbonyl or di-lower alkylamino-lower alkanoyl. Preferably, acyl is lower alkanoyl.

Acylamino represents e.g. lower alkanoylamino or lower alkoxycarbonylamino.

Acylamino-lower alkyl in R and R_1 is R_3-CONH-lower alkyl in which R_3 represents e.g. lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkyl-piperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkyl-piperidyl)-lower alkyl.

Lower alkanoyl represents e.g. C_1-C_7-alkanoyl including formyl, and is preferably C_2-C_4-alkanoyl such as acetyl or propionyl.

Aroyl represents e.g. benzoyl or benzoyl mono- or di-substituted by one or two radicals selected from lower alkyl, lower alkoxy, halogen, cyano and trifluoromethyl; or 1- or 2-naphthoyl; and also e.g. pyridylcarbonyl.

Lower alkoxycarbonyl represents preferably C_1-C_4-alkoxycarbonyl, e.g. ethoxycarbonyl.

Lower alkylene represents either straight chain or branched alkylene of 1 to 7 carbon

atoms and represents preferably straight chain alkylene of 1 to 4 carbon atoms, e.g. a methylene, ethylene, propylene or butylene chain, or said methylene, ethylene, propylene or butylene chain mono-substituted by C_1-C_3-alkyl (advantageously methyl) or disubstituted on the same or different carbon atoms by C_1-C_3-alkyl (advantageously methyl), the total number of carbon atoms being up to and including 7.

Esterified carboxyl is for example lower alkoxycarbonyl or benzyloxycarbonyl.

Amidated carboxyl is for example aminocarbonyl, mono- or di-lower alkylaminocarbonyl.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The compounds of the invention exhibit valuable pharmacological properties in mammals including man and are particularly useful as inhibitors of matrix-degrading metalloproteinase enzymes (= metalloproteinases).

As the compounds of the invention are inhibitors of stromelysin, gelatinase, collagenase and macrophage metalloelastase, and inhibit matrix degradation, they are particularly useful in mammals as agents for the treatment of e.g. osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, tumor metastasis, tumor invasion or progression, progression of HIV-infection and HIV-infection related disorders, atherosclerosis, osteoporosis and emphysema.

Illustrative of the matrix degrading metalloproteinase inhibitory activity, compounds of the invention prevent the degradation of cartilage caused by exogenous or endogenous stromelysin in mammals. They inhibit e.g. the stromelysin-induced degradation of aggrecan (large aggregating proteoglycan), link protein or type IX collagen in mammals.

Beneficial effects are evaluated in pharmacological tests generally known in the art, and as illustrated herein.

The above-cited properties are demonstrable in in vitro and in vivo tests, using advantageously mammals, e.g. rats, guinea pigs, dogs, rabbits, or isolated organs and tissues, as well as mammalian enzyme preparations. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally or parenterally, advantageously orally, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-5} molar and 10^{-10} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 0.1 and 50 mg/kg.

One test to determine the inhibition of stromelysin activity is based on its hydrolysis of Substance P using a modified procedure of Harrison et al (Harrison, R.A., Teahan J., and Stein R., A semicontinuous, high performance chromatography based assay for stromelysin, Anal. Biochem. 180, 110-113 (1989)). In this assay, Substance P is hydrolyzed by recombinant human stromelysin to generate a fragment, Substance P 7-11, which can be quantitated by HPLC. In a typical assay, a 10 mM stock solution of a compound to be tested is diluted in the assay buffer to 50 µM, mixed 1:1 with 8 µg recombinant human stromelysin (mol. wt. 45-47 kDa, 2 Units; where 1 Unit produces 20 mmoles of Substance P 7-11 in 30 minutes) and incubated along with 0.5mM Substance P in a final volume of 0.125 ml for 30 minutes at 37°C. The reaction is stopped by adding 10 mM EDTA and Substance P 7-11 is quantified on RP-8 HPLC. The IC_{50} for inhibition of stromelysin activity and Ki are calculated from control reaction without the inhibitor.

Illustrative of the invention, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride exhibits a Ki of 17 nM in this assay.

Stromelysin activity can also be determined using human aggrecan as a substrate. This assay allows the confirmation in-vitro that a compound can inhibit the action of stromelysin on its highly negatively-charged natural substrate, aggrecan (large aggregating prtoeoglycan). Within the cartilage, proteoglycan exists as an aggregate bound to hyaluronate. Human proteoglycan aggregated to hyaluronate is used as an enzyme substrate. The assay is set up in 96-well microtiter plates allowing rapid evaluation of compounds. The assay has three major steps:

1) Plates are coated with hyaluronate (human umbilical chord, 400 ug/ml), blocked with BSA (5 mg/ml), and then proteoglycan (human articular cartilage D1 - chondroitinase ABC digested, 2 mg/ml) is bound to the hyaluronate. Plates are washed between each step.

2) Buffers + inhibitor (1 to 5,000 nM) + recombinant human stromelysin (1-3 Units/well) are added to wells. The plates are sealed with tape and incubated overnight at 37°C. The plates are then washed.

3) A primary (3B3) antibody (mouse IgM, 1:10,000) is used to detect remaining fragments. A secondary antibody, peroxididase-linked anti-IgM, is bound to the primary antibody. OPD is then added as a substrate for the peroxidase and the reaction is stopped with sulfuric acid. The IC_{50} for inhibition of stromelysin activity is graphically derived and Ki is calculated.

Illustrative of the invention, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride exhibits an IC_{50} of 55 nM in this assay.

Collagenase activity is determined as follows: ninety six-well, flat-bottom microtiter plates are first coated with bovine type I collagen (35 ug/well) over a two-day period at 30°C using a humidified and then dry atmosphere; plates are rinsed, air dried for 3-4 hours, sealed with Saran wrap and stored in a refrigerator. Human recombinant fibroblast collagenase and a test compound (or buffer) are added to wells (total volume = 0.1 ml) and plates are incubated for 2 hours at 35°C under humidified conditions; the amount of collagenase used per well is that causing approximately 80% of maximal digestion of collagen. The incubation media are removed from the wells, which are then rinsed with buffer, followed by water. Coomasie blue stain is added to the wells for 25 minutes, removed, and wells are again rinsed with water. Sodium dodecyl sulfate (20% in 50% dimethylformamide in water) is added to solubilize the remaining stained collagen and the optical density at 570 nM wave length is measured. The decrease in optical density due to collagenase (from that of collagen without enzyme) is compared to the decrease in optical density due to the enzyme in the presence of test compound, and percent inhibition of enzyme activity is calculated. IC_{50}'s are determined from a range of concentrations of inhibitors (4-5 concentrations, each tested in triplicate), and K_i values are calculated.

Illustrative of the invention, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-

amino]-3-methylbutanamide hydrochloride exhibits a Ki of 62 nM in this assay.

The effect of compounds of the invention in-vivo can be determined in rabbits. Typically, four rabbits are dosed orally with a compound up to four hours before being injected intra-articularly in both knees (N=8) with 40 Units of recombinant human stromelysin dissolved in 20 mM Tris, 10 mM $CaCl_2$, and 0.15 M NaCl at pH 7.5. Two hours later the rabbits are sacrificed, synovial lavage is collected, and keratan sulfate (KS) and sulfated glycosaminoglycan (S-GAG) fragments released into the joint are quantitated. Keratan sulfate is measured by an inhibition ELISA using the method of Thonar (Thonar, E.J.-M.A., Lenz, M.E., Klinsworth, G.K., Caterson, B., Pachman, L.M., Glickman, P., Katz, R., Huff, J., Keuttner, K.E. Quantitation of keratan sulfate in blood as a marker of cartilage catabolism, Arthr. Rheum. 28, 1367-1376 (1985)). Sulfated glycosaminoglycans are measured by first digesting the synovial lavage with streptomyces hyaluronidase and then measuring DMB dye binding using the method of Goldberg (Goldberg, R.L. and Kolibas, L. An improved method for determining proteoglycan synthesized by chondrocytes in culture. Connect. Tiss. Res. 24,, 265-275 (1990)). For an i.v. study, a compound is solubilized in 1 ml of PEG-400, and for a p.o. study, a compound is administered in 5 ml of fortified corn starch per kilogram of body weight.

Illustrative of the invention, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride produces a 72% and 70% inhibition, respectively, in the release of KS and S-GAG fragments into the joint when given to rabbits at a dose of 30 mg/kg, 4 hours prior to the injection of human recombinant stromelysin.

Now, it has surprisingly been found that the compounds of the invention have a pronounced effect on tumor angiogenesis. Relevant tumors include human breast, lung, bladder, colon, prostate, skin and ovarian cancer. The growth of the tumors is inhibited, and even regression of the tumors is induced.

The effect on tumor angiogenesis can be determined e.g. in rats implanted with Walker 256 carcinoma in pellets to stimulate angiogenesis from vessels of the limbus, as described by Galardy et al, Cancer Res. 54, 4715 (1994).

The antitumor effect of the compounds of the invention can be determined e.g. by measuring the growth of human tumors implanted subcutaneously in Balb/c nude treated

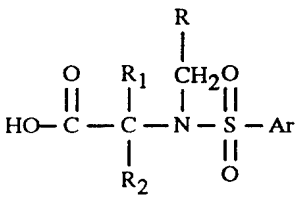
mice according to methodology well-known in the art in comparison to placebo treated mice.

Illustrative of the antitumor activity, the compound of example 1(a), N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride, administered at a dose of 30 mg/Kg p.o. twice daily to mice 7-17 days after implantation of human tumors, significantly inhibits the growth of e.g. estrogen dependent human breast carcinoma BT20 and MCF7, human bladder carcinoma T24, human colon carcinoma Colo 205, human lung adenocarcinoma A549 and human ovarian carcinoma NIH-OVCAR3. At oral doses of 30 and 60 mg/Kg twice daily, the compound of example 1(a), N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride, not only inhibits the growth of breast carcinoma MCF-7 but also induces regression of the tumor.

Further, it has now surprisingly been found that the compounds of the invention are also useful in the treatment of inflammatory demyelinating disorders of the nervous system in which myelin destruction or loss is involved, such as multiple sclerosis, optic neuritis, neuromyelitis optica (Devic's disease), diffuse and transitional sclerosis (Schilder's disease) and acute disseminated encephalomyelitis, also demyelinating peripheral neuropathies such as Landry-Guillain-Barre-Strohl syndrome for motor defects.

The effect on demyelinating disorders of the nervious system, such as multiple sclerosis, can be evaluated by measuring the reversal of experimental antioimmune encephalomyelitis in mice, e.g. as described by Gijbels et al, J. Clin. Invest. 94, 2177 (1994).

The compounds of formula I can be prepared e.g. by condensing a carboxylic acid of formula IV,



(IV)

or a reactive functional derivative thereof, wherein R, R_1, R_2 and Ar having meaning as

defined in claim 1, with hydroxylamine of formula V,

$$NH_2\text{-}OH \qquad (V)$$

optionally in protected form, or a salt thereof;

and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, carboxyl and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, carboxyl and hydroxy groups are those that can be converted under mild conditions into free amino and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1991.

In the processes cited herein, reactive functional derivatives of carboxylic acids represent, for example, anhydrides especially mixed anhydrides, acid halides, acid azides, lower

alkyl esters and activated esters thereof. Mixed anhydrides are preferably such from pivalic acid, or a lower alkyl (ethyl, isobutyl) hemiester of carbonic acid; acid halides are for example chlorides or bromides; activated esters for example succinimido, phthalimido or 4-nitrophenyl esters; lower alkyl esters are for example the methyl or ethyl esters.

Also, a reactive esterified derivative of an alcohol in any of the reactions cited herein represents said alcohol esterified by a strong acid, especially a strong inorganic acid, such as a hydrohalic acid, especially hydrochloric, hydrobromic or hydroiodic acid, or sulphuric acid, or by a strong organic acid, especially a strong organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylbenzene-sulfonic acid or 4-bromobenzenesulfonic acid. A said reactive esterified derivative is especially halo, for example chloro, bromo or iodo, or aliphatically or aromatically substituted sulfonyloxy, for example methanesulfonyloxy, 4-methylbenzenesulfonyloxy (tosyloxy).

In the above processes for the synthesis of compounds of the invention can be carried out according to methodology generally known in the art for the preparation of hydroxamic acids and derivatives thereof.

The synthesis according to the above process (involving the condensation of a free carboxylic acid of formula IV with an optionally hydroxy protected hydroxylamine derivative of formula V can be carried out in the presence of a condensing agent, e.g. 1,1'-carbonyldiimidazole, or N-(dimethylaminopropyl)-N'-ethylcarbodiimide or dicyclohexylcarbodiimide, with or without 1-hydroxybenzotriazole in an inert polar solvent, such as dimethylformamide or dichloromethane, preferably at room temperature.

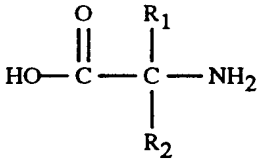
The synthesis involving the condensation of a reactive functional derivative of an acid of formula IV as defined above, e.g. an acid chloride or mixed anhydride with optionally hydroxy protected hydroxylamine, or a salt thereof, in presence of a base such as triethylamine can be carried out, at a temperature ranging preferably from about -78°C to +75°C, in an inert organic solvent such as dichloromethane or toluene.

Protected forms of hydroxylamine (of formula V) in the above process are those wherein the hydroxy group is protected for example as a t-butyl ether, a benzyl ether or tetrahydropyranyl ether, or as a trimethylsilyl derivative. Removal of said protecting groups is carried out according to methods well known in the art, e.g. hydrogenolysis or

acid hydrolysis. Hydroxylamine is preferably generated in situ from a hydroxylamine salt, such as hydroxylamine hydrochloride.

The starting carboxylic acids of formula IV can be prepared as follows:

An amino acid of formula VI

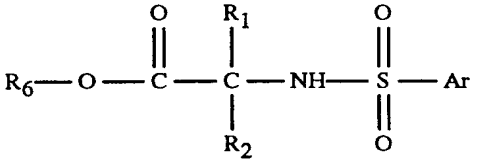


(VI)

wherein R_1 and R_2 have meaning as defined herein, is first esterified with a lower alkanol, e.g. methanol, in the presence of e.g. thionyl chloride to obtain an aminoester which is treated with a reactive functional derivative of the appropriate arylsulfonic acid of the formula VII

$$ArSO_3H \qquad (VII)$$

wherein Ar has meaning as defined hereinabove, e.g. with the arylsulfonyl chloride, in the presence of a suitable base such as triethylamine using a polar solvent such as tetrahydrofuran, toluene, acetonitrile to obtain a compound of the formula VIII



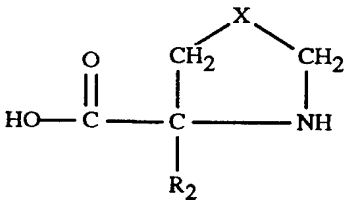
(VIII)

wherein R_1, R_2 and Ar have meaning as defined herein and R_6 is a protecting group, e.g. lower alkyl. Treatment thereof with a reactive esterified derivative of the alcohol of the formula IX

$$R\text{-}CH_2OH \qquad (IX)$$

wherein R has meaning as defined herein, such as the halide, e.g. the chloride, bromide or iodide derivative thereof, in the presence of an appropriate base, such as potassium

carbonate or sodium hydride, in a polar solvent such as dimethylformamide. The resulting compound corresponding to an ester of a compound of formula IV can then be hydrolyzed to the acid of formula IV, using standard mild methods of ester hydrolysis, preferably under acidic conditions. For compounds of formula Ia (wherein R and R_1 of formula I are combined) the starting materials are prepared by treating a carboxylic acid of formula X



(X)

or an ester thereof, wherein R_2 and X have meaning as defined above, with a reactive functional derivative of a compound of the formula $ArSO_3H$ (VII) under conditions described for the preparation of a compound of formula VIII.

The starting materials of formula VI, VII, IX and X are either known in the art, or can be prepared by methods well-known in the art or as described herein.

Optically active D-aminoacids of formula VI (the R-enantiomers) can be prepared according to methods known in the art, e.g. according to methods described in Tetrahedron Letters 28, 39 (1987), J. Am. Chem. Soc. 109, 7151 (1987) and J. Am. Chem. Soc. 110, 1547 (1988).

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures (preferably at or near the boiling point of the solvents used), and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed in situ under the reaction conditions, or in which

the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The invention also relates to any novel starting materials and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The hydroxamic acids or carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydro-abietylamine, brucine or strychnine)-salts.

Finally, acidic compounds of the invention are either obtained in the free form, or as a salt thereof.

Acidic compounds of the invention may be converted into salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit matrix-degrading metalloproteinases, and for the treatment of disorders responsive thereto, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbants, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75 %, preferably about 1 to 50 %, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable

pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art.

The pharmaceutical formulations contain an effective matrix-degrading metalloproteinase inhibiting amount of a compound of the invention as defined above either alone, or in combination with another therapeutic agent, e.g. an anti-inflammatory agent with cyclooxygenase inhibiting activity, or other antirheumatic agents such as methotrexate, each at an effective therapeutic dose as reported in the art. Such therapeutic agents are well-known in the art.

Examples of antiinflammatory agents with cyclooxygenase inhibiting activity are diclofenac sodium, naproxen, ibuprofen, and the like.

In conjunction with another active ingredient, a compound of the invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 10 and 1000 mg, advantageously between about 25 and 250 mg of the active ingredient.

The present invention also relates to methods of using the compounds of the invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting the matrix-degrading metalloproteinases, e.g. stromelysin, collagenase and macrophage metalloelastase, for inhibiting tissue matrix degradation, and for the treatment of matrix-degrading metalloproteinase dependent conditions as described

herein, e.g. osteoarthritis, also tumors (tumor growth, tumor metastasis, progression or invasion), pulmonary disorders, and the like described herein. Tumors (carcinomas) include human breast, lung, bladder, colon, prostate and ovarian cancer, and skin cancer, including melanoma and Kaposi's sarcoma.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art. The concentration for $[\alpha]_D$ determinations is expressed in mg/ml.

Example 1: The following compounds for which, surprisingly, the new use of treating e.g. human breast, lung, bladder, colon, prostate, skin and ovarian cancer as well as treating e.g. multiple sclerosis has been found have already been disclosed in EP-A-606 046 and/or WO-A-96/00214:

(a) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, the hydrochloride, the L-tartaric acid salt, the methanesulfonic acid salt and the maleic acid salt thereof,

(b) N-Hydroxy-2(S)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride,

(c) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4-methylpentanamide hydrochloride,

(d) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino]-4-methyl-pentanamide,

(e) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](piperonyl)amino]-4-methylpentan-amide,

(f) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-4-methylpentan-

amide,

(g) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-3-methylbutanamide hydrochloride,

(h) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4,4-dimethylpentanamide hydrochloride,

(i) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-cyclohexylacetamide hydrochloride,

(j) N-Hydroxy-2(R)-[[(2,3-dihydrobenzofuran)-5-sulfonyl]-(3-picolyl)amino]-3-methylbutanamide hydrochloride,

(k) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride,

(l) N-Hydroxy-2(R)-[[4-ethoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride,

(m) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-cyclohexylacetamide hydrochloride,

(n) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-cyclohexylacetamide hydrochloride,

(o) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]-2-cyclohexylacetamide hydrochloride,

(p) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanamide,

(q) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-phenylacetamide,

(r) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-t-butylacetamide,

(s) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]-4-methyl-

pentanamide,

(t) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-3-methylbutanamide,

(u) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4,4-dimethylpentanamide,

(v) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl(benzyl)amino]-3-hydroxypropanamide,

(w) N-hydroxy-3-[4-methoxybenzenesulfonyl]-5,5-dimethylthiazolidine-4(S)-carboxamide,

(x) N-hydroxy-1-[4-methoxybenzenesulfonyl]-pyrrolidine-2(S)-carboxamide,

(y) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)-ethyl]acetamide,

(z) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[2-(4-morpholino)-ethyl]acetamide,

(aa) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-[2-(4-morpholino)-ethyl]acetamide dihydrochloride,

(ab) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[2-(4-morpholino)-ethyl]acetamide dihydrochloride,

(ac) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride,

(ad) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-thiomorpholino)-ethyl]acetamide,

(ae) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-methylthiazol-4-ylmethyl]acetamide,

(af) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[6-chloropiperonyl]-

acetamide,

(ag) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-pyrazolyl)methyl]-acetamide,

(ah) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[3-picolyl]acetamide dihydrochloride,

(ai) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(aj) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(ak) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(al) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(am) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(an) N-hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,

(ao) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]propionamide,

(ap) methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionoate.

(aq) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-thiomethylbutyramide,

(ar) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-(methylsulfonyl)-butyramide,

(as) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionamide,

(at) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-benzylacetamide,

(au) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N,N-dimethylamino)-hexanamide hydrochloride,

(av) N-hydroxy-2-(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-6-(N,N-dimethylamino)-hexanamide dihydrochloride,

(aw) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-6-(N,N-dimethylamino)-hexanamide dihydrochloride,

(ax) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino]hexanamide hydrochloride,

(ay) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-tetrahydrothiopyran,

(az) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-tetrahydropyran,

(ba) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)-amino]-cyclohexane,

(bb) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)amino]-cyclopentane,

(bc) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-cyclohexane,

(bd) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolyl-amino]-cyclopropane hydrochloride,

(be) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-piperidine,

(bf) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[dimethylaminoacetyl]-piperidine hydrochloride,

(bg) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl(benzyl)-amino]-1-[3-picolyl]-piperidine dihydrochloride,

(bh) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[carbomethoxymethyl]-piperidine hydrochloride,

(bi) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-piperidine trifluoroacetate;

(bj) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[t-butoxycarbonyl]-piperidine;

(bk) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[methyl-sulfonyl]-piperidine;

(bl) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[methyl]piperidine hydrochloride,

(bm) 4-[N-Hydroxycarbamoyl]-4-[[methoxybenzenesulfonyl](benzyl)amino]-1-[morpholinocarbonyl]piperidine,

(bn) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[4-picolyl]piperidine dihydrochloride,

(bo) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]acetamide,

(bp) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]acetamide,

(bq) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexylmethyl)amino]acetamide,

(br) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexyl)amino]acetamide,

(bs) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](phenethyl)amino]acetamide,

(bt) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-methylbutyl)amino]acetamide,

(bu) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](sec-butyl)amino]acetamide,

(bv) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](tert-butyl)amino]acetamide,

(bw) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]acetamide,

(bx) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-chlorobenzyl)amino]acetamide,

(by) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isopropyl)amino]acetamide,

(bz) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methylbenzyl)amino]acetamide,

(ca) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-phenyl-1-propyl)amino]acetamide

(cb) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbutyl)amino]acetamide,

(cc) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-cyclohexylethyl)amino]acetamide,

(cd) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]acetamide

(ce) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2,2,2-trifluoroethyl)amino]acetamide,

(cf) N-Hydroxy-2-[[benzenesulfonyl](isobutyl)amino]acetamide,

(cg) N-Hydroxy-2-[[4-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide,

(ch) N-Hydroxy-2-[[4-chlorobenzenesulfonyl](isobutyl)amino]acetamide,

(ci) N-Hydroxy-2-[[4-methylbenzenesulfonyl](isobutyl)amino]acetamide,

(cj) N-Hydroxy-2-[[4-fluorobenzenesulfonyl](isobutyl)amino]acetamide,

(ck) N-Hydroxy-2-[[benzenesulfonyl](benzyl)amino]acetamide,

(cl) N-Hydroxy-2-[[4-nitrobenzenesulfonyl](isobutyl)amino]acetamide,

(cm) N-Hydroxy-2-[[4-(tert)-butylbenzenesulfonyl](isobutyl)amino]acetamide,

(cn) N-Hydroxy-2-[[4-methylsulfonylbenzenesulfonyl](isobutyl)amino]acetamide,

(co) N-Hydroxy-2-[[3-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide,

(cp) N-Hydroxy-2-[[2,4,6-trimethylbenzenesulfonyl](isobutyl)amino]acetamide,

(cq) N-Hydroxy-2-[[2,5-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(cr) N-Hydroxy-2-[[3,4-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(cs) N-Hydroxy-2-[[2,4,6-triisopropylbenzenesulfonyl](isobutyl)amino]acetamide,

(ct) N-Hydroxy-2-[[3,5-dimethylisoxazole-4-sulfonyl(benzyl)amino]acetamide,

(cu) N-Hydroxy-2-[[2,4-dimethylthiazole-5-sulfonyl(benzyl)amino]acetamide,

(cv) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methoxybenzyl)amino]acetamide,

(cw) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]acetamide,

(cx) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]acetamide,

(cy) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]acetamide,

(cz) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-piperidinylethyl)amino]acetamide,

(da) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetamide,

(db) N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-picolyl)amino]acetamide hydrochloride,

(dc) N-hydroxy-2-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino] acetamide,

(dd) N-hydroxy-2-[[4-methoxybenzenesulfonyl](3,4,5-trimethoxybenzyl)-amino]acetamide,

(de) N-hydroxy-2-[[4-methoxybenzenesulfonyl](3-methoxybenzyl)amino]acetamide,

(df) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-[4-morpholino]ethyl)amino]acetamide,

(dg) N-Hydroxy-2-[[4-aminobenzenesulfonyl](isobutyl)amino]acetamide,

(dh) N-Hydroxy-2-[[4-dimethylaminobenzenesulfonyl](isobutyl)amino]acetamide,

(di) N-hydroxy-2-[[4-hexyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dj) N-Hydroxy-2-[[4-ethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(dk) N-Hydroxy-2-[[4-butyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dl) N-Hydroxy-2-[[4-(3-methyl)butyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dm) N-Hydroxy-2-[[4-heptyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dn) N-Hydroxy-2-[[4-(cyclohexylmethoxy)benzenesulfonyl](isobutyl)amino]acetamide,

(do) N-Hydroxy-2-[[4-isopropyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dp) N-Hydroxy-2-[[4-ethoxyethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(dq) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetamide,

(dr) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-5-tetrazolyl)-methyl]acetamide,

(ds) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(5-tetrazolyl)-

methyl]acetamide,

(dt) N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]-2-[(5-tetrazolyl)-methyl]acetamide,

(du) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, and the hydrochloride thereof,

(dv) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide and the hydrochloride thereof,

(dw) N-(benzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(dx) N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(dy) N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide,

(dz) N-(2,4-dimethoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(ea) N-(2-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(eb) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3(R)-(3-picolyl-oxy)-butanamide dihydrochloride,

(ec) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclo-hexylacetamide hydrochloride,

(ed) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-(2-pyridyl)ethyl)amino]-2-cyclohexylacetamide,

(ee) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-(3-pyridyl)propyl)-

amino]-2-cyclohexylacetamide,

(ef) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-methyl-pyrid-5-ylmethyl)-amino]-2-cyclohexylacetamide,

(eg) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-tetrahydropyranmethyl)-amino]-2-cyclohexylacetamide

(eh) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidinyl)acetamide hydrochloride

(ei) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[N-(dimethylaminoacetyl)-4-piperidinyl]acetamide,

(ej) N-hydroxy-2-(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(3-pyrrolidinyl)-acetamide hydrochloride,

(ek) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(N-t-butoxycarbonyl-3-pyrrolidinyl)-acetamide,

(el) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(4-tetrahydropyranyl)-acetamide hydrochloride,

(em) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(3-picolyl)amino]-2-(trans-4-hydroxycyclohexyl)-acetamide hydrochloride,

(en) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(trans-4-dimethyl-aminocyclohexyl)acetamide hydrochloride,

(eo) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[trans-4-(dimethylaminoacetylamino)cyclohexyl]acetamide hydrochloride,

(ep) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-tetrahydrofuranyl)-acetamide,

(eq) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(3-picolyl)amino]-2-(2-tetra-

hydrofuranyl)-acetamide,

(er) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-tetra-hydrofuranyl)-acetamide,

(es) N-hydroxy-2(S)-[(4-methoxybenzenesulfonyl)(3-picolyl)amino]-2-(2-tetra-hydrofuranyl)-acetamide,

(et) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(trans-4-hydroxy-2-tetrahydrofuranyl)acetamide,

(eu) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-oxacyclo-octyl)acetamide,

(ev) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)-amino]-2-(4-oxacyclo-heptyl)acetamide hydrochloride,

(ew) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-cyclooctyl-acetamide hydrochloride,

(ex) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-oxohexahydro-azepin-5-yl)acetamide hydrochloride, diastereoisomer A,

(ey) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-oxohexahydro-azepin-5-yl)acetamide hydrochloride, diastereoisomer B,

(ez) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-oxohexahydro-azepin-5-yl)acetamide, diastereoisomer A,

(fa) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-oxohexa-hydroazepin-5-yl)acetamide, diastereoisomer B,

(fb) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3,4-dimethoxy-butanamide,

(fc) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3-methoxy-3-(N-

tert-butoxycarbonyl-4-piperidyl)propionamide,

(fd) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(N-ethoxy-carbonyl-4-piperidyl)-acetamide hydrochloride,

(fe) N-hydroxy-2-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(tetrahydro-2H-pyran-2-yl)-acetamide hydrochloride,

(ff) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(cis-4-hydroxy-cyclohexyl)-acetamide hydrochloride,

(fg) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[trans-4-(ethoxy-carbonylamino)cyclohexyl]-acetamide,

It is to be understood that each compound mentioned in example 1 may be used either in the neutral form, or in the form of a pharmaceutically acceptable salt, e.g. in the specific salt form mentioned in the above list.

Example 2: N-Hydroxy-2-[[2-thiophenesulfonyl](isobutyl)amino]acetamide is prepared by coupling isobutylamine with 2-thiophenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in EP-A-606 046 (example 16) for the compound of example 1(bo) of the present application.

Example 3: A solution of N-benzyloxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)-amino]-3-hydroxy-4-methylpentanamide (125 mg) in ethanol (100 ml) is hydrogenated in the presence of 5% palladium on charcoal (100 mg) at room temperature and atmospheric pressure to yield N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-3-hydroxy-4-methyl-pentanamide, m.p. 81-82°C.

The starting material is prepared as follows:

(R)-3-hydroxy-4-methyl-2-amino pentanoic acid methyl ester, prepared according to methodology described by Evans in Tetrahedron Letters 28, 39 (1987) and J. Am. Chem. Soc. 109, 7151 (1981) from isobutyraldehyde, is converted, according to methodology in previous examples, to 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino] 3-hydroxy-4-methylpentanoic acid.

A solution of 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino] 3-hydroxy-4-methyl-pentanoic acid (1.4 g) in methylene chloride (3.5 ml) is treated with 2,6-lutidine (1.21 ml) and tert-butyl-dimethylsilyl trifluoromethanesulfonate (2.03 ml) at 0°C. The solution is stirred at 0°C for 4 hours, then at room temperature for 2 hours, poured into sodium bicarbonate solution (10.0 ml) and extracted with ether. The resulting product is purified by column chromatography on silica gel using gradients of ethyl acetate/hexane as eluent to obtain 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino] 3-(tert-butyl-dimethylsilyl-oxy)-4-methylpentanoic acid tert-butyl-dimethylsilyl ester. Treatment of the ester (1.2 g) with potassium carbonate (285 mg) in THF water (1:1) for 30 minutes at 0° under nitrogen, acidification and extraction with ethyl acetate yields 2(R)-[(4-methoxybenzene-sulfonyl)(benzyl)amino] 3-(tert-butyl-dimethylsilyloxy)-4-methylpentanoic acid.

To a solution of 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-3-(tert-butyl-dimethylsilyloxy)-4-methylpentanoic acid (0.5 g) in methylene chloride (10 ml) are added O-benzylhydroxylamine hydrochloride (0.154 g), 1-hydroxy-pyridobenzotriazole (HOPT, 0.131 g), N-methylmorpholine (0.371 ml) at room temperature. Then 1-(3-dimethyl-aminopropyl)-3-ethyl-carbodiimide (0.370 g) is added at 0°C and the reaction mixture is stirred at room temperature overnight under nitrogen. The reaction mixture is diluted with ethyl acetate and water, and the ethyl acetate extract is washed with 1N hydrochloric acid, sodium bicarbonate solution, water and brine. The organic phase is dried, evaporated to dryness and the resulting product is purified by flash chromatography using ethyl acetate/hexane gradients as eluent to yield N-benzyloxy-2(R)-[(4-methoxybenzene-sulfonyl)(benzyl)amino]-3-tert-butyl-dimethylsilyloxy) 4-methylpentanamide.

A solution of the above (0.4 g) in acetonitrile (6.4 ml) is treated with 48% hydrogen fluoride (0.25 ml) and stirred at room temperature for 4 hours. Workup in the usual manner and purification by chromatography on silica gel with ethyl acetate/hexane gradients as eluent yields N-benzyloxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)-amino]-3-hydroxy-4-methylpentanamide as an oil.

Similarly prepared are:

(a) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3-hydroxy-pentanamide, m.p. 129-131°C;

(b) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)-amino] 3-hydroxy-4-methyl-pentanamide, m.p. 69-71°C;

(c) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-3-hydroxy-4-methyl-pentanamide, m.p. 81-82°C;

(d) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3-hydroxy-octanamide, m.p. 123-125°C;

(e) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3-hydroxy-5-methyl-hexanamide, m.p. 97-99°C.

Example 4: Similarly prepared to the previous examples and similarly as described in EP-A-606 046 and/or WO-A-96/00214 for the compounds of examples 1(a) to 1(fg) of the present application are:

(a) N-hydroxy-2(R)-[(3-fluoro-4-methoxybenzenesulfonyl) (3-picolyl)amino]-3-methyl-butanamide hydrochloride, $[\alpha]_D^{25}$ + 33.85 (c 10.39 mg/ml, CH_3OH);

(b) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-cyclopentyl-acetamide hydrochloride, m.p. >140° dec.; $[\alpha]_D^{25}$ + 27.9 (c 9.4, CH_3OH);

(c) N-hydroxy-4-[(4-methoxybenzenesulfonyl)(benzyl)amino]-N-(methoxycarbonyl-methyl)-piperidine-4-carboxamide hydrochloride, m.p. 183.5-185°C;

(d) N-benzyloxy-4-[(4-methoxybenzenesulfonyl)(n-benzyl)amino]-N-(methoxy-carbonylmethyl)-piperidine-4-carboxamide, m.p. 52.5-55°C;

(e) N-hydroxy-2-[[4-methoxybenzensulfonyl] (benzyl)amino]-2-[2-thienylthio)methyl] acetamide by starting the synthesis with β-(2-thienylthio)alanine (prepared according to the procedure of J.Am.Chem.Soc. 110, 2237, (1988);

(f) N-hydroxy-2-[[4-methoxybenzenesulfonyl] (benzyl)amino]-2-[(2-furanylthio)methyl]-acetamide by starting the synthesis with β-(2-furanylthio)alanine (prepared according to the procedure of J.Am.Chem.Soc. 110, 2237 (1988);

(g) N-hydroxy-2-[[4-methoxybenzenesulfonyl] (benzyl)amino]-2-[(phenylthio)methyl]-acetamide by starting the synthesis with β-(phenylthio)alanine (prepared according to the procedure of J.Am.Chem.Soc. 110, 2237 (1988);

Example 5: Preparation of 3000 capsules each containing 25 mg of the active ingredient, for example, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride:

Active ingredient	75.00 g
Lactose	750.00 g
Avicel PH 102 (microcrystalline cellulose)	300.00 g
Polyplasdone XL (polyvinylpyrrolidone)	30.00 g
Purified water	q.s.
Magnesium stearate	9.00 g

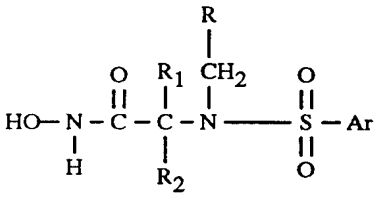
The active ingredient is passed through a No. 30 hand screen.

The active ingredient, lactose, Avicel PH 102 and Polyplasdone XL are blended for 15 minutes in a mixer. The blend is granulated with sufficient water (about 500 mL), dried in an oven at 35°C overnight, and passed through a No. 20 screen.

Magnesium stearate is passed through a No. 20 screen, added to the granulation mixture, and the mixture is blended for 5 minutes in a mixer. The blend is encapsulated in No. 0 hard gelatin capsules each containing an amount of the blend equivalent to 25 mg of the active ingredient.

Claims:

1. Use of a compound of formula I



(I)

(a) wherein

Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_{10}-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy) lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl or N-acyl(hexahydroazepinyl, piperidyl or pyrrolidinyl), C_5-C_{10}-oxacycloalkyl, C_5-C_{10}-thiacycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-cycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-thiacycloalkyl, (hydroxy- or oxo-) C_5-C_{10}-

oxacycloalkyl, (amino, mono- or dialkylamino or acylamino)-C_5-C_{10}-cycloalkyl, 2-oxo(pyrrolidinyl, piperidyl or hexahydroazepinyl), (carbocyclic or heterocyclic aryl)-(thio, sulfinyl or sulfonyl)-lower alkyl;

R_2 is hydrogen or lower alkyl;

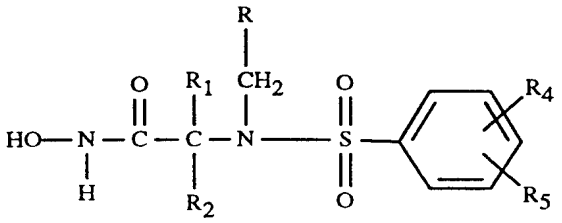
(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof;

(for the manufacture of a medicament) for the treatment of a tumor selected from human breast carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, prostate carcinoma, skin carcinoma and ovarian carcinoma.

2. Use according to claim 1, where the compound used is a compound of formula II



(II)

wherein
R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl,

[(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_5-C_8-cycloalkyl, C_5-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, piperidyl, N-lower alkylpiperidyl, or acylamino-lower alkyl represented by R_3-CONH-lower alkyl, pyrrolidinyl, hexahydroazepinyl or N-lower alkyl (pyrrolidinyl or hexahydroazepinyl), C_5-C_7-oxacycloalkyl, C_5-C_7-thiacycloalkyl, hydroxy or oxo-cyclohexyl, (amino, mono- or di-lower alkylamino) cyclohexyl or 2-oxohexahydroazepinyl; phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl; heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thienyl and furanyl, each unsubstituted or substituted by lower alkyl;

R_2 is hydrogen;

R_3 in R_3-CONH-lower alkyl is lower alkyl, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)-lower alkyl;

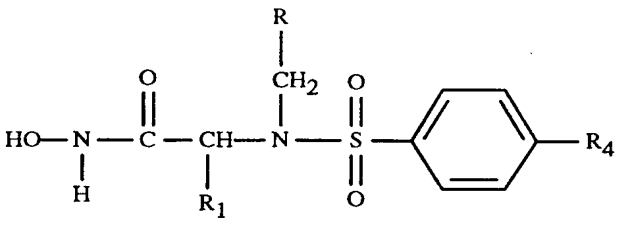
R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

R_5 is hydrogen, lower alkyl or halogen;

or R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

3. Use according to claim 1, where the compound used is a compound of formula III



(III)

wherein R represents lower alkyl, trifluoromethyl, C_5-C_7-cycloalkyl, (oxa or thia)-C_4-C_5-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R_1 represents hydrogen, lower alkyl, C_5-C_8-cycloalkyl, monocyclic carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl-lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, di-lower alkylamino-lower alkyl, (N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino)-lower alkyl, C_5-C_7-oxacycloalkyl, (hydroxy, oxo or di-lower alkylamino) cyclohexyl, R_3-CONH-lower alkyl, phenyl-thio-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl, heterocyclic aryl-thio-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl, thienyl and furanyl, each unsubstituted or substituted by lower alkyl; R_3 represents lower alkyl, carbocyclic aryl, heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; R_4 represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

4. Use according to claim 1, where the compound used is a compound of formula III wherein R represents monocyclic carbocyclic aryl or monocyclic heterocyclic aryl; R_1 and R_4 have meaning as defined above; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

5. Use according to claim 1, where the compound used is a compound of formula III wherein R represents heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents lower alkyl, cyclohexyl, 2- or 3-tetrahydrofuranyl, or R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower

alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; and R_4 represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

6. Use according to claim 1, where the compound used is a compound of formula III wherein R represents 2-, 3- or 4-pyridyl or phenyl; R_1 represents C_1-C_4-alkyl, cyclohexyl, 2- or 3-tetrahydrofuranyl, (phenyl-, thienyl- or furanyl-)thiomethyl, or R_3-CONH-C_1-C_4-alkyl wherein R_3 represents di-C_1-C_4-alkylamino-C_1-C_4-lower alkyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

7. Use according to claim 1, where the compound used is a compound of formula III wherein R represents 3-pyridyl or 4-pyridyl; R_1 represents isopropyl, cyclohexyl or 2-tetrahydrofuranyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

8. Use according to claim 3, where the compound used is a compound wherein the asymmetric carbon to which R_1 is attached is assigned the (R)-configuration.

9. Use according to claim 1, where the compound used is N-hydroxy-2(R)-[[4-methoxy-benzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, a pharmaceutically acceptable prodrug derivative thereof or a pharmaceutically acceptable salt thereof.

10. Use according to claim 1, where the compound used is N-hydroxy-2(R)-[[4-methoxy-benzenesulfonyl](3-picolyl)amino]-3-methylbutanamide or a pharmaceutically acceptable salt thereof.

11. Use according to claim 1, where the compound used is N-hydroxy-2(R)-[[4-methoxy-benzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetamide or a pharmaceutically acceptable salt thereof.

12. Use according to claim 1, where the compound used is N-hydroxy-2(R)-[(4-methoxy-benzenesulfonyl)(4-picolyl)amino]-2-(2-tetrahydrofuranyl) acetamide or a pharmaceutically acceptable salt thereof.

13. Use according to any one of claims 1 to 12, where a medicament is manufactured which induces regression of the tumor.

14. Use according to any one of claims 1 to 12, where a medicament is manufactured which is useful for the treatment of the tumor angiogenesis.

15. A method of treating a tumor selected from human breast carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, prostate carcinoma, skin carcinoma and ovarian carcinoma which comprises administering to a subject in need thereof a therapeutically effective amount of N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(3-picolyl)-amino]-3-methylbutanamide or a pharmaceutically acceptable salt thereof.

16. A method according to claim 15, where regression of the tumor is induced.

17. A method according to claim 15, where the tumor angiogenesis is treated.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCI/EP 96/02418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/18 A61K31/33 A61K31/495 A61K31/535 A61K31/54
A61K31/445 A61K31/40 A61K31/335 A61K31/38 A61K31/55
A61K31/47 A61K31/42 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,95 35275 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 28 December 1995 see page 1 see page 21	1-17
X	EP,A,0 606 046 (CIBA GEIGY AG) 13 July 1994 see page 8	1-17
X,P	US,A,5 506 242 (MACPHERSON ET AL.) 9 April 1996 see column 1	1-17
X,P	WO,A,96 00214 (CIBA-GEIGY AG) 4 January 1996 see page 12	1-17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1996	02.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/02418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,95 35276 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 28 December 1995 see page 1 see page 17 ---	1-17
A	PROC.NATL.ACAD.SCI.USA, vol. 92, no. 2, January 1995, pages 462-466, XP000578245 N.C.GONNELLA ET AL.: "Bioactive conformation of stromelysin inhibitors determined by transferred nuclear Overhauser effects" see the whole document -----	1-17

1

national application No.

PCT/EP 96/02418

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 15-17, and partially claims 1-14, realte to a method of treatment of the human/animal body, the search has been based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4,8,14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

As a result of the use of expressions like "heterocyclic" a complete search is virtually impossible.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...al Application No
PCT/EP 96/02418

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9535275	28-12-95	AU-B-	2746595	15-01-96
		AU-B-	2746695	15-01-96
		WO-A-	9535276	28-12-95
EP-A-0606046	13-07-94	US-A-	5455258	03-10-95
		AU-B-	5265593	04-05-95
		CA-A-	2112779	07-07-94
		FI-A-	940012	07-07-94
		HU-A-	70536	30-10-95
		JP-A-	6256293	13-09-94
		NO-A-	940038	07-07-94
		NZ-A-	250517	26-10-95
		US-A-	5506242	09-04-96
		ZA-A-	9400048	11-08-94
US-A-5506242	09-04-96	US-A-	5455258	03-10-95
		AU-B-	2536995	19-01-96
		WO-A-	9600214	04-01-96
		AU-B-	5265593	04-05-95
		CA-A-	2112779	07-07-94
		EP-A-	0606046	13-07-94
		FI-A-	940012	07-07-94
		HU-A-	70536	30-10-95
		JP-A-	6256293	13-09-94
		NO-A-	940038	07-07-94
		NZ-A-	250517	26-10-95
		ZA-A-	9400048	11-08-94
WO-A-9600214	04-01-96	US-A-	5506242	09-04-96
		AU-B-	2536995	19-01-96
WO-A-9535276	28-12-95	AU-B-	2746595	15-01-96
		AU-B-	2746695	15-01-96
		WO-A-	9535275	28-12-95